T cell receptors were mated with allogeneic C57BL/6 males (K^b); expression of K^b on fetal tissues significantly influenced the mother's T cell repertoire and reactivity. Pregnant females with a high frequency of anti-K^b T cells were unable to reject K^b-bearing tumor cells implanted subcutaneously. Upon parturition, alloreactivity was regained, and the tumor cells were eliminated. Thus, immune privilege at the maternal-fetal interface is expressed systemically, is actively acquired, and can be transient (as is pregnancy).

What is the biological importance of immune privilege? The results of Tafuri *et al.* (*16*) suggest that immune privilege is necessary for the success of pregnancy. Immune privilege in the anterior chamber of the eye is critical to the avoidance of stromal keratitis, a blinding disease of the cornea that accompanies ocular infection with herpes simplex virus–type 1 (HSV-1). In mice the incidence and severity of HSV-1 keratitis rises dramatically in eyes in which privilege has been lost (*17*). Similarly, immune privilege protects against experimental autoimmune uveoretinitis evoked by eye-specific autoantigens (*18*). Finally, orthotopic corneal allografts are the most successful of all solid-organ transplants in humans, because the eye is a privileged site and the cornea is a privileged tissue. Corneal grafts placed in eyes that have lost immune privilege suffer acute rejection (*19*). Restoration of privilege to such "high-risk" eyes should allow acceptance of corneal allografts that restore vision. Similar strategies may promote the success of other solid-tissue allografts and prevent autoimmune and immunopathogenic diseases of privileged sites and tissues.

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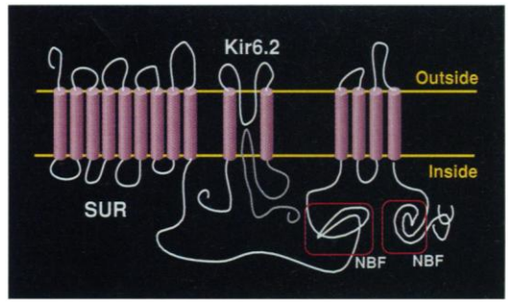
UPDATE

ATP-Sensitive K^+ Channels: Paradigm Lost, Paradigm Regained

Louis H. Philipson

Potassium channels set the resting membrane potential in many kinds of cells and thereby regulate their electrical activity and ion transport. One kind of K^+ channel, K_{ATP}, is inhibited by cytosolic adenosine triphosphate (ATP), thus coupling the metabolic state of the cell to membrane electrical events. The currents carried by these channels have been most thoroughly studied in pancreatic islet ß cells, where they regulate insulin secretion in response to glucose.



Partners. The inward rectifier Kir6.2 combines with the sulfonylurea receptor (SUR) to generate K_{ATP}.

Clues to the molecular identity of the K_{ATP} channels were revealed when the sulfonylurea receptor (SUR) was cloned (*1*) and mutations in SUR were found in several cases of persistent hyperinsulinemia and hypoglycemia of infancy (PHHI) (*2*). Sulfonylureas, the principal treatment for adult onset diabetes, block ß cell K_{ATP} channels. Yet SUR itself does not form the ion-conducting part of the K_{ATP} channel. Instead, as proposed in our previous Perspective (*3*), sulfonylurea-sensitive K_{ATP} is likely formed by an interaction between an inward-rectifier K^+ channel and SUR, which is a member of the ATP-binding cassette protein family. In this issue of *Science*, Inagaki and coworkers have verified this idea and found the right match for SUR—an inward rectifier K^+ channel called Kir6.2 (*4*).

Until now, K^+ channel subunit architecture has been defined by the minimal structure: the P (pore) domain and two flanking transmembrane segments that can be part of a much larger protein (see figure). In the current paradigm, functional channels are formed from tetrameric arrays of homologous subunits (*5*). The parsimonious assumption would be that K_{ATP} would also fit this paradigm. Instead, Inagaki *et al.* have shown that SUR, a protein with no obvious function other than that of binding drugs (*1*, *3*), confers both ion channel activity and K_{ATP}-like pharmacological sensitivities on Kir6.2. A new member of the inward rectifier K^+ channel family, Kir6.2 cannot conduct ions when expressed alone. This dependence on other molecules for optimal activity is an extreme version of a property displayed by some other inward rectifiers—the enhancement of their current by coexpression with similar proteins or G proteins (*6*, *7*).

What is the relation between SUR and its channel? Ten or more inward-rectifier channels may aggregate to form a large complex (*6*); does SUR physically associate with such a complex?

The reconstitution of K_{ATP}-like functions by combining SUR with an inward rectifier of minimal intrinsic activity is more than a curious paradox; it also recalls a model recently described for regulation of the protein critical in cystic fibrosis, CFTR (*8*). Higgins has reviewed evidence suggesting that CFTR and other ATP-binding cassette-containing proteins may be regulators of channels and pumps. We now have our first glimpse of the new paradigm for K_{ATP}.

The author is in the Department of Medicine and is on the Committee on Cell Physiology, University of Chicago, Chicago, IL 60637, USA. E-mail: l-philipson@uchicago.edu

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